15 Special Syndromes: Serotonin Syndrome, Neuroleptic Malignant Syndrome, and Catatonia

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15.1 Introduction

Serotonin syndrome (SS), neuroleptic malignant syndrome (NMS), and catatonia are often seen in the context of the acute psychiatric unit and have serious consequences if not recognized early in the geriatric population. The following vignette shows how the syndromes overlap in presentation, and are challenging to diagnose and to differentiate, especially in the geriatric patient. Figure 15.1 illustrates in overview, the assessment and management of the special conditions SS, NMS, and catatonia. A more specific introduction to each syndrome is offered below.

15.2 Vignette

An 81-year-old man presented to hospital due to the onset of disorientation within the prior 24 hours. He was irritable, agitated, and repeated, "Sam, Sam, where are you?" He lived with his wife and needed minimal assistance with activities of daily living (ADLs). Three years ago, he was diagnosed with Parkinson disease and began treatment with carbidopa/levodopa 25/100 mg po t.i.d. He was also prescribed amlodipine 25 mg po daily for hypertension. He had no known past psychiatric history nor any illicit substance use or alcohol abuse.

Six weeks prior to admission, he was diagnosed with complicated bereavement, after the sudden death of his young grandson, Sam. Family members reported that the patient began hallucinating the voice of his deceased grandson. He was started on fluoxetine 20 mg po daily but unable to tolerate it, and a week prior to admission he was switched to escitalopram 10 mg po daily. Within that same week, he was diagnosed with a urinary tract infection (UTI), and a course of ciprofloxacin was started. The day before admission, the patient developed confusion, anxiety, headache, dizziness, restlessness, shivering, tremor, dysarthria, diarrhea, and diaphoresis.

On admission, his blood pressure was 130/75 mm Hg, heart rate 116 beats/min, and axillary temperature 98.6 F. The complete blood count, electrolytes, glucose, calcium, liver, kidney, creatine phosphokinase (CPK) levels, and thyroid function tests were within normal limits. Electrocardiogram (ECG) was normal. Computed tomography (CT) of the head showed no acute abnormalities. A provisional diagnosis of major depressive disorder secondary to complicated bereavement was made. Physical symptoms were considered manifestations of anxiety, and escita-

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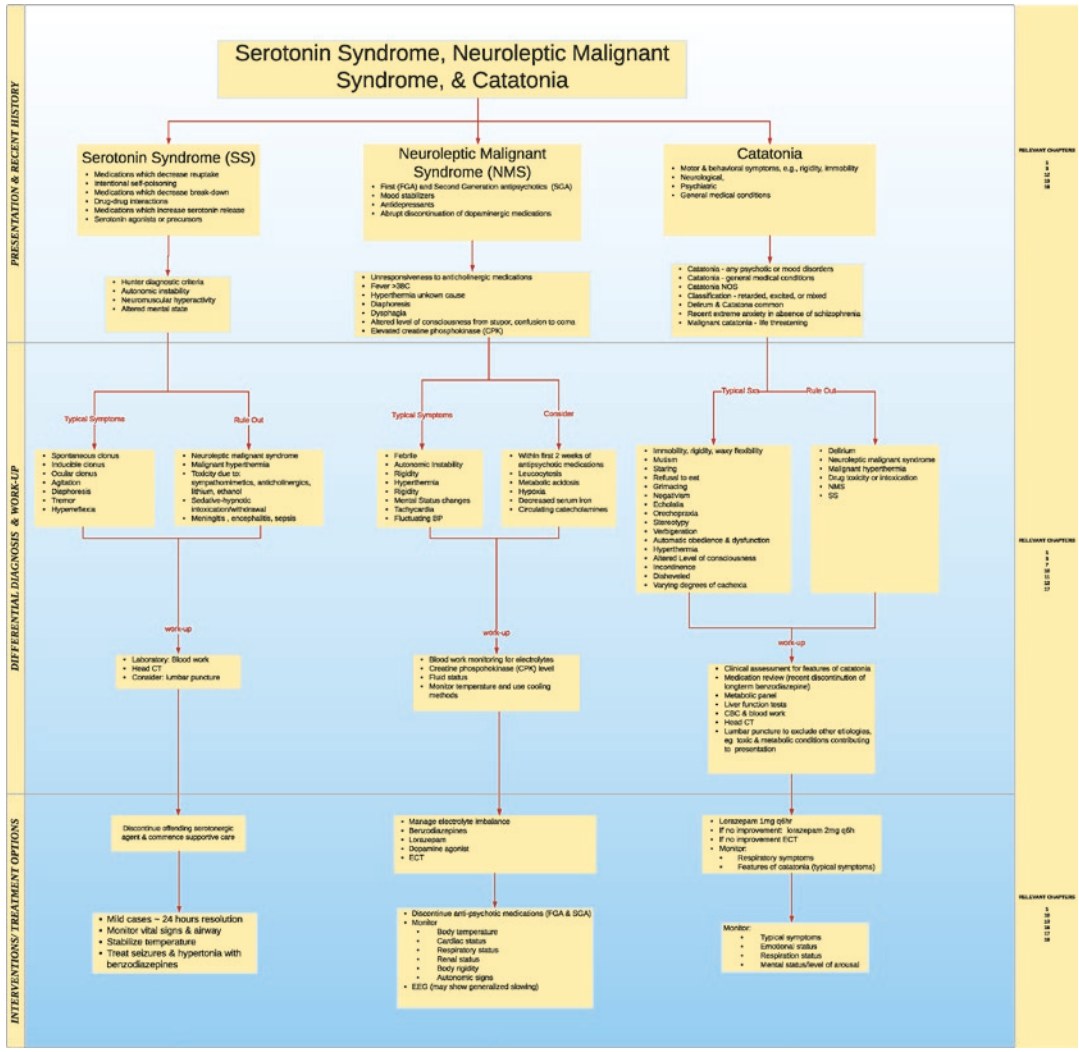


Fig. 15.1 Special syndromes: serotonin syndrome, neuroleptic malignant syndrome, and catatonia

lopram was increased to 20 mg po daily; olanzapine 5 mg daily was added to treat hallucinations.

On the second hospitalization day, his physical status worsened, with increased confusion, mydriasis, tachycardia, hyperreflexia, myoclonus, muscular rigidity, and inability to walk, but there were no focal neurological findings. A diagnosis of SS was offered using Hunter Criteria [1], and all serotonergic agents were discontinued, and he was prescribed lorazepam 1 mg t.i.d. On the third hospitalization day, carbidopa/levodopa (C/L) was discontinued due to the possibility that this medication contributed to his auditory hallucinations. Over hospitalization days number 3–7, the patient became more alert to his environment.

On hospitalization day #8, he developed hyper-rigidity, temperature of 100.58 °F, and CPK rose to 1622 IU/L; and his blood pressure was labile. These characteristic symptoms and signs confirmed the diagnosis of NMS. Olanzapine was discontinued and CPK levels were drawn every 4 hours.

Comment NMS is a potentially lethal condition, described in patients with idiopathic Parkinson

disease (PD), after long-term dopaminergic medications are stopped abruptly or moderately decreased. If patients with PD develop severe rigidity, stupor, and hyperthermia, levodopa withdrawal should be suspected and the dopaminergic drug restarted as soon as possible to prevent rhabdomyolysis and renal failure. The vignette patient was also at a high risk for NMS due to the introduction of olanzapine due to dopamine receptor antagonism. The patient was transferred to ICU, where levodopa was reintroduced, while olanzapine was withdrawn. The increase in temperature resolved the next day; rigidity gradually resolved over the next 10 days, and serum CPK levels began to fall. Escitalopram was reintroduced gradually to treat his depressive symptoms.

The differential diagnoses at admission included:

1. *Delirium associated with PD.* Parkinson disease is a progressive neurodegenerative disorder, with three cardinal features: resting tremor, rigidity, and bradykinesia. It mostly affects the geriatric age group. Of note, delirium has been reported in 5–25% of Parkinson disease patients treated with levodopa. High doses of levodopa can also lead to confusion and psychosis [2].
2. *SS*: SS typically presents with autonomic changes, delirium, and neurological findings of hyperreflexia/clonus, particularly in association with recent medication changes; e.g., introduction or increased doses of Selective Serotonin Reuptake Inhibitors (SSRIs). In the vignette, the diagnosis of SS was worth considering. Clinical presentation in the vignette was dynamic, and therefore, catatonia, SS, nor NMS could not be ruled out initially. Several concurrent factors in the vignette patient's presentation clouded the diagnosis:
   - An acute change from baseline
   - Autonomic changes (i.e., shivering, diaphoresis)
   - Psychiatric symptoms (i.e., anxiety, delirium)
   - Neurological symptoms (i.e., headache, confusion, dizziness, dysarthria, gait disturbances)
   - Gastrointestinal symptom (i.e., diarrhea)
   - History of sub-acute symptoms consistent with a depressive disorder (i.e., complicated grief disorder)
   - Comorbid neurological condition (i.e., Parkinson disease)

The primary psychiatric diagnoses were considered only *after* exclusion of other systemic etiologies. The patient was initially evaluated for delirium, with the delirium protocol (Chap. 12: Delirium). Cerebrovascular events were important diagnoses to rule out, due to the risk factors of neurological symptoms, autonomic symptoms, advanced age, and hypertension. Isolated dizziness and headache symptoms are common clinical contexts for missed cerebrovascular disease. A risk of misdiagnosis is much greater when presenting neurologic complaints are mild, nonspecific, or transient [3]. It was important to consider the possibility of medication adverse effects, such as adverse effect of antibiotics, as an etiological factor for delirium. The polypharmacy and recent medication changes were also risk factors for delirium. Treatment with ciprofloxacin complicated the differential diagnosis of the vignette patient's acute symptomatology. Tandon et al. [4] reviewed 39 studies of fluoroquinolones and found the most commonly reported adverse effects were nausea, vomiting, diarrhea, headache, dizziness, and rash.

In a study by Halkin, 1988, overall rates of adverse reactions associated with fluoroquinolones (ciprofloxacin in the vignette) have been shown to be 4–8%, and adverse reactions necessitated discontinuation of the therapy in 1–2.6% of patients. Patterns of organ system involvement and of signs and symptoms were quite similar, with gastrointestinal effects predominating (nausea, vomiting, diarrhea, or abdominal pain in 1–5% of the patients), followed by effects on the central nervous system (dizziness, headache, and/or insomnia in 0.1–0.3% of the patients), and skin (0.5–2.2% of the patients). Elevation in levels of hepatic enzymes occurred in 1.8–2.5% of the patients, azotemia in 0.2–1.3%, and eosinophilia in 0.2–2.0%. These adverse effects were reversible after drug withdrawal and were

generally not dose-dependent [5]. More recently, Tandan et al. [4] have confirmed many of the central nervous system (CNS) and gastrointestinal adverse events associated with fluoroquinolones, including nausea, vomiting, diarrhea, headache, dizziness, and [4].

15.3 Serotonin Syndrome (SS)

15.3.1 Introduction

SS is an adverse medication effect, characterized by excess serotonergic agonism in the central and peripheral nervous systems. It can result from therapeutic drug use, intentional self-poisoning, or drug-drug interactions. It is a well-known and predictable drug reaction; hence, it is also often preventable and usually treatable. Its early recognition can be challenging because the syndrome includes a spectrum of clinical symptoms ranging from mild to severe and life-threatening.

SS is not an idiosyncratic drug reaction or allergy; it is rather a predictable and direct response to increased concentration levels of serotonergic activity in the body. SS has been described classically as a triad of distinct clinical symptoms – *autonomic instability, neuromuscular hyperactivity, and altered mental status/delirium*. In its early stages, a patient seldom presents with all three of the triad of symptoms simultaneously, and the condition can be missed or misdiagnosed. Frequently, the symptoms are mild and self-limiting; however, in severe cases, and if the syndrome is not identified early in its course, progression can lead to organ failure and death [6]. Figure 15.2 provides a summary of the clinical triad of symptoms associated with SS.

15.3.2 Epidemiology

Approximately 15% of patients who overdose on SSRIs develop SS [7]. But SS often goes unrecognized and unreported, so the incidence of SS is difficult to establish. Almost 85% of family physicians reported that they were not aware of SS as a clinical entity [8]. Some of the clinical symptoms associated with SS, such as diarrhea, fever,

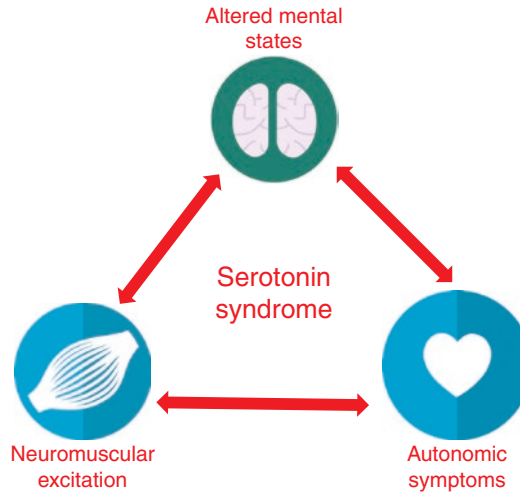


Fig. 15.2 Serotonin syndrome symptoms

and tremors, may be dismissed by patients and clinicians as unrelated to medication use, or misdiagnosed as another condition, such as an infection or another psychiatric disorder [6].

SS has been recognized in all age groups, including children and newborns. However, the aged have increased vulnerability to SS, due to changes in drug metabolism which occur with aging (e.g., a decline in liver volume), susceptibility for increased polymorphism in P450 cytochromes, and loss of inducibility of metabolizing enzymes. A decline in drug clearance in heart and kidney disease may lead to a hyper-serotonergic state with common medications such as SSRI and serotonin and norepinephrine reuptake inhibitors (SNRIs) [9] (Chap. 3: Pharmacological Overview). Geriatric patients are also at a higher risk for polypharmacy that can lead to complex drug interactions that result in SS. Diet influences drug metabolism, and a high prevalence of protein-calorie malnutrition in sick hospitalized geriatric patients may add a risk for the development of SS. Trauma and ill health can also have substantial effects on enzymes of drug metabolism in geriatric patients [9].

15.3.3 Etiology

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter concentrated within neurons located in the raphe nuclei. Serotonin neurons

play a part in sleep-wakefulness cycles, mood, emotional and food-seeking behaviors, and thermoregulation. All drugs that directly or indirectly increase central serotonin neurotransmission at postsynaptic receptors 5-hydroxytryptamine 1A (5-HT1A) and 5-hydroxytryptamine 2A (5-HT2A) can produce SS.

Many psychotropic and nonpsychotropic drugs modulate serotonin receptors. SS is associated with excessive levels of serotonin, which can be altered by dosage timing, dosage frequency, drug interactions, drug overdoses – accidental and intentional – and inadequate washout periods between medication changes [10]. This phenomenon has implications for medication revision strategies such as drug discontinuation, tapering, and switching (Chap. 17: Medication Strategies).

Wang et al. [10] described five mechanisms by which commonly prescribed medications can alter serotonin levels and cause SS:

- *Decreased serotonin breakdown*: Medication classes include monoamine oxidase inhibitors, antibiotics including linezolid and tedizolid and methylene blue, procarbazine, and Syrian rue may decrease serotonin breakdown, and thereby, increased serotonin availability.
- *Decreased serotonin reuptake:*
  - SSRIs: fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram, sertraline
  - SNRIs: venlafaxine, duloxetine, milnacipran
  - Tricyclic antidepressants (TCAs): clomipramine, imipramine, amitriptyline
  - The herbal remedy, St. John's wort
  - Opioids: meperidine, buprenorphine, tramadol [11], tapentadol, dextromethorphan
  - Antiepileptics: valproate, carbamazepine
  - Antiemetics: ondansetron, granisetron, metoclopramide
- *Increased serotonin precursors or agonists*: Agents include tryptophan, lithium, fentanyl, and lysergic acid diethylamide (LSD).
- *Increased serotonin release within the central nervous system*: amphetamines, anorectics (e.g., fenfluramine), dexfenfluramine and phentermine, cocaine and methylenedioxymethamphetamine (ecstasy), as drugs of abuse.
- *Drug-drug interactions*: Medications that inhibit drug metabolism can cause a higher serum concentration of serotonin. Specifically, inhibitors of CYP2D6 and CYP3A4, including the antibiotics erythromycin and ciprofloxacin, the antifungal fluconazole, and the antiretroviral ritonavir.

Table 15.1 lists pharmacological mechanisms which can lead to increased central serotonin transmission [10].

15.3.4 Clinical Description

As noted above, the SS is classically composed of a triad of symptoms: *neuromuscular excitation, altered mental status, and autonomic dysfunction.* Many patients will not exhibit the full clinical triad, and symptoms may not occur simultaneously; altered mental status and autonomic dysfunction are present in roughly 40% of the cases and neuromuscular excitation in 50% [12]. SS may also present in mild, moderate, and severe forms, with most cases mild and self-limiting [13]. The mild form can present with sub-acute symptoms, whereas the most severe SS is life-threatening and, within hours of onset, can rapidly progress to organ failure. Patients typically come

Table 15.1 Pharmacological mechanisms leading to increased central serotonin transmission

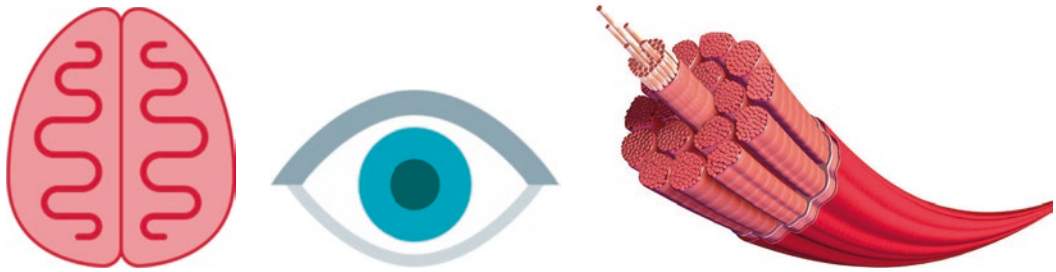
- Augmentation of serotonin synthesis
- Increased serotonin release
- Inhibition of serotonin uptake
- Inhibition of serotonin metabolism leads to direct stimulation of postsynaptic serotonin receptors

to attention within 24 hours of overdose, dose adjustment, and/or drug initiation [14]. The spectrum of presentation includes aspects within the triad of symptoms (neuromuscular excitation, altered mental status, and autonomic dysfunction) but differs in severity. Figure 15.3 summarizes the differential diagnosis of SS.

Mild SS starts with neuromuscular excitation, seen as hyperreflexia, tremor, and myoclonus, altered mental status in the form of anxiety, restlessness, and insomnia, and is associated with autonomic dysfunction as diaphoresis, mydriasis, and tachycardia. The symptoms of toxicity with serotonergic agents arise within 1 hour of a precipitating event in approximately 30% of patients and within 6 hours in 60% [14].

Moderate symptoms of SS include *opsoclonus* (uncontrolled eye movements which are rapid, involuntary, unpredictable, conjugate, and fast), spontaneous or inducible clonus, neuromuscular excitation, agitation, hypertension, hyperthermia (< 40 °C, < 104 °F), hyperactive bowel sounds, and diarrhea, nausea, and vomiting.

Severe cases of SS include neuromuscular excitation in the form of rigidity, respiratory failure, tonic-clonic seizures, altered mentation (manifested as coma or delirium), autonomic dysfunction with severe hyperthermia (> 40 °C, > 104 °F), and fluctuations in blood pressure (Chapter: Delirium). If rigidity is not treated properly, the resulting hyperthermia can lead to cell damage and rhabdomyolysis, myoglobinuria, renal failure, metabolic acidosis, acute respiratory distress syndrome, disseminated intravascular coagulation, and death [15]. A distinct neurological finding with SS is that spontaneous/induced clonus and hyperreflexia are both more pronounced in the lower extremities than in the upper extremities [1]. Table 15.2 summarizes the SS spectrum of severity.



Mental state changes	Autonomic instability	Neuromuscular abnormalitis
• Agitation • Pressured speech • Confusion	• Tachycardia • Shivering • Mydriasis • Diaphoresis • Diarrhea	• Hyper-reflexia (lower extremities > upper) • Clonus • Tremor • Mydriasis • Seizure

Risk factors:
- history of exposure to a serotonergic drug

Presence of one or more of the following:
- spontaneous clonus
- inducible clonus with agitation and diaphoresis
- ocular clonus with agitation and diaphoresis
- tremor and hyperreflexia
- hypertonia
- temperature over 38 °C / 100.4 F with ocular or inducible clonus

Fig. 15.3 Hunter serotonin toxicity criteria

Table 15.2 SS severity spectrum

Serotonin Syndrome	*Mild*	*Moderate*	*Severe*
Neuromuscular excitation	Hyperreflexia Tremor Myoclonus	Opsoclonus Spontaneous/inducible clonus (pronounced in lower limbs)	Rigidity Respiratory Failure Tonic-clonic Seizures
Altered mental status	Anxiety Restlessness Insomnia	Agitation	Delirium Confusion Coma
Autonomic dysfunction	Diaphoresis Mydriasis Tachycardia	Hypertension Hyperthermia (< 40C or < 104F) Hyperactive bowel sounds Diarrhea Nausea Vomiting	Severe Hyperthermia (> 40C or > 104F) Fluctuating BP

15.3.5 Diagnostic Evaluation

Serotonin syndrome more commonly presents on a continuum rather than in clear-cut clinical stages, and the diagnosis can be difficult to recognize, easily missed, or misdiagnosed. The Hunter diagnostic criteria, based predominantly on physical signs and observable symptoms, were developed to use clear markers to identify SS. Using a decision tree algorithm, the Hunter criteria include spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor, and hyperreflexia in the context of serotonin exposure [16], which determine the likelihood of SS. Figure 15.3 summarizes the key features of the Hunter serotonin toxicity criteria. In the case vignette, the patient's medications, escitalopram, olanzapine, and levodopa were discontinued, and he was given lorazepam 1 mg t.i.d.

The clinical symptoms in the vignette likely occurred following the introduction of the antidepressant escitalopram, which began without an adequate washout period from fluoxetine. Hence, the initial presentation may have in fact been SS – mild and most likely missed and misdiagnosed as major depressive disorder (MDD) and anxiety. Increase in escitalopram, in combination with olanzapine, which also has serotoninergic activity, likely worsened SS (Chap. 17: Medication Interventions).

15.3.6 Differential Diagnosis

The differential diagnosis of SS includes, among other conditions, NMS; malignant hyperthermia; toxic levels of sympathomimetics, anticholinergics, lithium, and ethanol; sedative-hypnotic withdrawal; meningitis; intracranial bleeding; or encephalitis [16] (Chap. 10: Alcohol and Substance intoxication and withdrawal).

In an aging patient, the anticholinergic burden of the medication regimen and possible toxicity must always be considered due to the pervasive use of medications with anticholinergic properties. The anticholinergic syndrome typically presents with hyperthermia, agitation, confusion, mydriasis, dry mucous membranes, urinary retention, constipation, and decreased bowel sounds. As opposed to those in the SS, muscular tone and reflexes are normal in anticholinergic toxicity.

Workup should include a routine metabolic panel, liver function tests, complete blood count (CBC), a head CT, and, in some cases, a lumbar puncture to exclude other etiologies like toxic and metabolic conditions attributing to the presentation [16]. Figure 15.4 summarizes the differential diagnosis for SS.

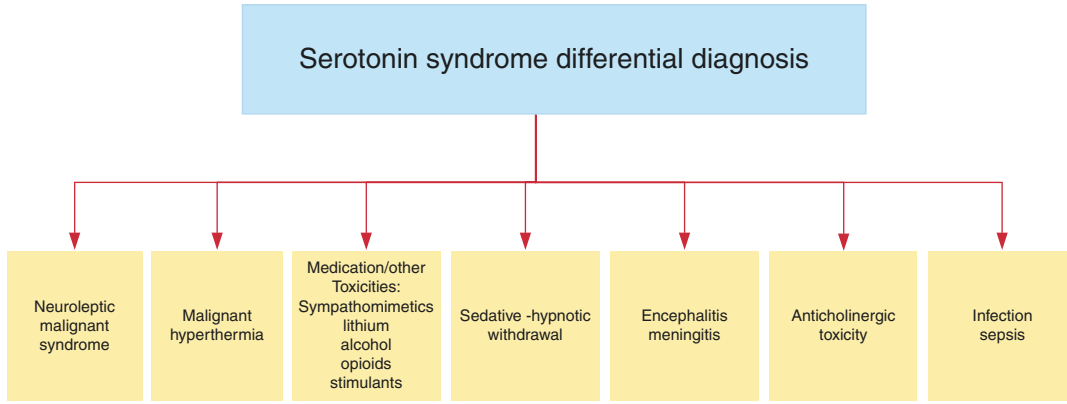


Fig. 15.4 SS differential diagnosis

15.3.7 Treatment

The first steps for management of SS should include discontinuation of all serotonergic agents and provision of supportive care; mild forms of SS can resolve within the first 24 hours. Special attention should be paid to vital signs and airway to dictate further management. Hyperthermia should be managed with cooling measures and the physician should avoid the use of antipyretics, as SS temperature instability is not centrally mediated, but is rather secondary to increased muscle tone. Increased muscle tone leading to myoclonus, seizures, and hypertonia should be managed by benzodiazepines. Consider intubation and muscle paralysis with severe degrees of muscle rigidity.

Mason et al. [14] reviewed the role of antiserotonergic agents like cyproheptadine for the reversal of SS in human case reports. Cases demonstrated resolution occurring within the first 1 hour. Treatment is, however, limited to those who are able to swallow, but this agent may also be administered by nasogastric tube. The initial cyproheptadine dose of 4–8 mg can be titrated up to a maximum of 20 mg daily dictated by clinical improvement. Further human trials to determine the efficacy of this medication are needed to establish guidelines.

15.4 Neuroleptic Malignant Syndrome (NMS)

15.4.1 Introduction

NMS is an idiosyncratic drug reaction, of uncertain etiology, wherein patients become hyperthermic, display signs of autonomic instability, rigidity, and delirium. It can be fatal if not recognized and treated promptly [15].

Delay and Deniker [17] recognized NMS for the first time, and described it as a syndrome of extrapyramidal symptoms with four principal symptoms: hyperthermia, rigidity, mental status changes, and autonomic dysfunction. Another description of the distinct clinical features of NMS includes rigidity unresponsive to anticholinergic medications, hyperthermia of *unknown* cause, diaphoresis, dysphagia, changes in level of consciousness ranging from confusion to coma, and elevated CPK levels [18].

15.4.2 Epidemiology

The overall incidence of NMS ranges between 0.02% and 3.23% [18]. NMS is less common in older adults for unknown reasons. Men are approximately 50% more likely than women to be

Table 15.3 First-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) associated with NMS

Antipsychotics	
First Generation	Second Generation
• Flupentixol	• Clozapine
• Haloperidol	• Olanzapine
• Fluphenazine	• Risperidone
• Thioridazine	• Quetiapine
• Chlorpromazine	• Aripiprazole
• Trifluoperazine	• Paliperidone
• Loxapine	• Asenapine
• Periciazine	• Ziprasidone
• Methotrimeprazine	
• Prochlorperazine	
• Zuclopenthixol	

diagnosed at any age [19]. Antipsychotic use has been the most common etiological factor; other implicated drug classes include mood stabilizers (e.g., lithium, carbamazepine), antidepressants (e.g., paroxetine, sertraline, amitriptyline), and antiemetic agents (e.g., metoclopramide) [20].

The proposed mechanism for SSRI/TCA leading to NMS is based on the pharmacodynamics of SSRIs, in which an excess of serotonin inhibits dopamine release, worsening the hypodopaminergic state [21]. The TCA mechanism with clomipramine primarily works on serotonin, while amitriptyline and imipramine are norepinephrine−/serotonin-acting agents, which would cause a hypodopaminergic state similar to SSRIs.

NMS has also been associated with use of the SGAs as well as FGAs. The rate of NMS resulting from SGA administration is similar to the rate resulting from administration of FGAs [20]. The risk is not well known; however, it has been cited as 0.02–2.44% [22]. Table 15.3 lists First Generation and Second Generation antipsychotics commonly associated with NMS.

15.4.3 NMS Precipitating Factors

Careful monitoring is necessary to recognize NMS symptoms promptly and initiate early intervention (Chap. 3: Pharmacological Overview). Situations which have the potential to precipitate NMS include:

1. The use of more than one antipsychotic at a time. FGA have been associated with NMS in approximately 68% of NMS cases, and almost 72% of these cases were co-medicated with an SGA. Median length of exposure to an SGA prior to the onset of NMS was 23 days, while the median length of exposure to a FGA before onset was 6 days. Mortality rate was 11% for SGA-induced NMS and 12% for FGA-induced NMS [20].
2. Age: Independent predictor of mortality; each 10-year increase in age is associated with a 40% increased odds of mortality [23]. Antipsychotic treatment is hazardous in the aged population even with SGAs.
3. Major neurocognitive disorders, especially Lewy body type, are at risk of antipsychotic hypersensitivity when exposed to antipsychotics. Extrapyramdal symptoms and NMS have been attributed to a depletion of nigrostriatal dopaminergic neurons and acetylcholinergic receptors [24], although other explanations have been offered. NMS has developed in patients with major neurocognitive disorder with Lewy bodies, even when treated with SGAs [25–28].
4. Abrupt cessation or reduction in the dose of dopaminergic medications, such as levodopa in Parkinson disease, may precipitate NMS. A rapid switch from one type of dopamine receptor agonist to another has also been associated with NMS. An abrupt withdrawal of medications to treat Parkinson disease, which do not possess *direct* dopaminergic activity, such as amantadine (a tricyclic amine) and tolcapone (a catechol-O-methyltransferase – COMT) inhibitor [29], can result in NMS. A common complication of NMS has been rhabdomyolysis (30.1%), and of those patients, 30% developed acute kidney injury, out of which 5.9% underwent hemodialysis. Other complications included respiratory failure requiring ventilator support, pneumonia, and sepsis.

The current overall reported mortality rate for NMS is between 4% and 30%, with a 50% mortality rate for cases in which renal failure develops [30]. There is a slight increase of NMS reported cases in summer seasons, due to higher likelihood of increased heat and dehydration [30]. Depot antipsychotic-induced NMS lasts twice as long as NMS induced by oral medications [30]. Table 15.4 shows a summary of common inciting and predisposing factors associated with NMS.

15.4.4 Etiology of NMS

The etiology of NMS has been explained as an adverse effect of antipsychotic drugs which function as dopamine (D2) receptor blockers. Approximately 0.5–1.0% of those treated with FGA and SGA will develop NMS within the first 2 weeks, during which antipsychotics are titrated to their therapeutic dose [15]. Patients taking carbamazepine, valproic acid, or those who have undergone rapid discontinuation of levodopa, amantadine, and benzodiazepines are also at risk [31–33].

Early in its recognition, NMS was viewed as an example of malignant catatonia, secondary to antipsychotic use. Similarly, dantrolene and dopamine agonists were proposed as treatment because the symptoms of NMS were so similar to those of malignant hyperthermia [34]. Consensus recommendations advised treatment with benzodiazepines and electroconvulsive therapy (ECT) if treatment had failed with benzodiazepines [33, 35–38].

The original hypothesis that malignant hyperthermia and NMS each had a different etiology has become less prominent. The finding that NMS can be provoked by medications *other than* antipsychotics supports the notion that this syndrome was not due solely to antipsychotics and/or dopamine blockade. Other instigating medications include disulfram, corticosteroids, phencyclidine, abrupt withdrawal of anticholinergic and antihistamine drugs, and phenelzine with lithium or dothiepin [15].

15.4.5 Clinical Description

NMS remains an unpredictable and potentially life-threatening neurologic condition that requires early identification and proper medical management to ensure improved patient outcomes. As mentioned, it most often presents within the first 2 weeks of antipsychotic initiation during drug titration to therapeutic doses. Patients typically present with hyperthermia >100.4 °F, autonomic instability, rigidity, mood alterations, and delirium. The DSM-5 identifies defining characteristics of NMS to include "lead pipe rigidity," most often resistant to antiparkinsonian agents, and other symptoms summarized in Table 15.5.

Table 15.4 Inciting or predisposing factors in neuro malignant syndrome

N	• Dehydration
	• Malnutrition
	• Exhaustion
M	• Intramuscular injection of antipsychotics
	• Advanced age
	• Neuropsychiatric disorders
	• Traumatic brain injuriy
	• Antipsychotic dose increases
	• Neurodegenerative brain disease (e.g., MNCD)
S	• Infections
	• Ethanol (EtOH) intoxication
	• HIV infection
	• Concomitant use of lithium, anticholinergic agents, and some antidepressant agents

Table 15.5 DSM-5: NMS and signs

• Rigidity • Tremor • Sialorrhea • Akinesia • Dystonia • Trismus • Myoclonus • Dysarthria • Dysphagia • Rhabdomyolysis • Extremely high temperatures • Creatine kinase levels 4x higher than upper limit of normal • Significant impairment in mentation • Altered levels of consciousness from delirium to coma.		• Dazed apperance - may be mistaken for a catatonic like picture • Autonomic dysregulation - tachycardia > 25% baseline • Diaphoresis • Fluctuations in blood pressure - > 20mm Hg diastolic or > 25mm Hg systolic • Urinary incontinence • Pallor • Respiratory distress - tachypnea > 50% above baseline • Metabolic acidosis • Hyper-metabolism • Restricted chest wall expansion, • Aspiration pneumonia • Pulmonary emboli - may lead to respiratory arrest

15.4.6 Differential Diagnosis of NMS

A workup for NMS needs to exclude infectious, metabolic, substance-related, or other neuropsychiatric conditions, but no specific laboratory test is yet specific to NMS. Laboratory results will show leukocytosis, metabolic acidosis, hypoxia, decreased serum iron, and an elevation in creatine phosphokinase (CPK) and circulating catecholamines. EEG demonstrates a generalized slowing, while cerebrospinal fluid (CSF) and neuroimaging are nonspecific.

15.4.7 Treatment

Mild cases of NMS should be treated conservatively with fluid replacement, correction of electrolyte imbalance, and normalization of body temperature with active cooling methods. Cardiac, respiratory, and renal status should be carefully monitored [18, 39]. A trial with lorazepam 0.5–1.0 mg IM q4–6 hours has been demonstrated to be effective as a primary approach by Woodbury and Woodbury [40]. Severe cases of NMS may require the use of a dopamine agonist to correct the depleted dopaminergic state of the body. Velamoor [41] considers dopaminergic agents when temperatures fall between 38.3° and 40 °C (100.9 °F and 104 °F). Bromocriptine 2.5 mg or amandine 100 mg every 8 hours continued for 10 days with a gradual taper [18]. If temperatures exceed 40 °C, IV dantrolone 2–3 mg/kg body weight may be warranted to decrease the muscle spasticity and rigidity [41]. If ineffective, treatment with ECT is recommended [33, 35–38], especially in cases where delirium, rigidity, and catatonia have not resolved [39].

15.5 Catatonia

15.5.1 Introduction

Catatonia is a complex neuropsychiatric condition characterized by particular motor and behavioral signs and symptoms that can manifest as a consequence of many neurologic, psychiatric, and/or general medical conditions, which was first described in 1874 [42]. For decades, catatonia was thought to be a subtype of schizophrenia and appeared this way in the early versions of the DSM [43]. Because of its complexity and variation in presentation, the DSM-5 has since modified the phenomenological approach to define catatonia with specifiers. These include: catatonia as a result of all psychotic, depressive, and bipolar disorders, as a result of non-CNS general medical conditions, or as a syndrome *not otherwise specified*. It is characterized by psychomotor, autonomic, and behavioral abnormalities [44], occurring in general medical, neurological, and psychiatric conditions as well as due to medications and illicit substances.

15.5.2 Epidemiology of Catatonia

Psychiatrists and other physicians tend to underrecognize catatonia [45] despite the reported high prevalence rate in some studies. Prevalence varies between 5% and 50.8% in acute psychiatric admissions, based on the diagnostic method used [33]. The prevalence of catatonia is estimated to be 5–18% in inpatient psychiatric units, 12% in drug-naïve patients with first episode psychosis, 3.3% in a neurology/neuropsychiatric tertiary care inpatient

unit, 3.8% in the intensive care unit, 1.6–1.8% in psychiatry consultation-liaison services, and 8.9% in geriatric patients referred for psychiatric consultation [46].

Catatonia has been commonly associated with depressive and bipolar disorders, particularly manic episodes [42, 47, 48]. The prevalence of catatonia due to a general medical condition may also vary from 20% to 39% [49]. Catatonia in older patients frequently appears in association with a systemic medical condition rather than secondary to a primary psychiatric presentation [50]. Delirium and catatonia can often coexist at the same time in a patient, this of course makes the diagnosis of catatonia difficult to recognize as a syndrome separate from delirium. Catatonia was present in at least 12% of patients with delirium [46] (Chap. 12: Delirium). For example, delirium and catatonic features are indistinct and often difficult to delineate [51]. In the geriatric population, superimposed cognitive and somatic conditions (i.e., emotional dysregulation caused by a physical symptom) may complicate the symptom presentation [52]. Immobility associated with major neurocognitive disorder has been postulated as a catatonic state, and some authors suggest that this may respond to lorazepam [53].

15.5.3 Etiology

No consensus exists about the specific pathophysiological mechanism underlying catatonia. Often patients have retrospectively reported feeling extreme levels of anxiety immediately prior to a catatonic episode. Because of these consistent reports, one theory of the neuropathology is that catatonia is the result of intense anxiety that reflects a functional GABA deficit [54]. This supports its response to benzodiazepines by acting on the GABA-A receptor ion channels, the mechanism thought to be responsible for the treatment of catatonia. However, patients with schizophrenia who have had a catatonic episode do not endorse the same heightened levels of anxiety as those with depressive or bipolar disorders report [43].

Another pathophysiological theory is that catatonia is a movement disorder. Rasmussen et al. [43] report the overlapping nature of catatonia as parkinsonism, a dysfunction within the basal ganglia. In support, functional imaging has demonstrated altered activity in the orbitofrontal, prefrontal, parietal, and motor cortical regions in catatonia [55]. This author reinforces that GABA-A binding is also reduced in catatonic patients, motor and mood symptoms coincide with GABA-A binding abnormalities, and cortical abnormalities in catatonic patients resolve with lorazepam.

15.5.4 Clinical Description of Catatonia

Catatonia is subtyped into three clinical forms: retarded, excited, or mixed. Table 15.6 summarizes the presentations of catatonia, with malignant catatonia requiring urgent assistance [56].

Immobility and mutism are the most commonly identified signs of catatonia, observed in 90.6% and 84.4% of catatonic patients, respectively [57]. Rasmussen et al. [43] report incontinence, disheveled appearance, and varying degrees of cachexia as other common symptoms. In another report, the most prevalent catatonic signs were excitement (64.3%), verbigeration (61.9%), negativism (59.5%), immobility/stupor (57.1%), and staring (52.4%) [42].

15.5.5 Treatment

Benzodiazepines remain the gold standard treatment for catatonia. The intravenous route is preferred because of quick onset of action, length of action, and ease of administration. Initial dose should be 1 mg of lorazepam IV q6h. If no improvement, lorazepam should be increased to 2 mg q6h. Maintenance doses should total 6–8 mg daily with divided doses occurring every 6–8 hours for 2–3 days, which should be followed by oral treatment and tapered before discontinuing to prevent relapse into catatonia. During this

Table 15.6 Various presentations of catatonia

CATATONIA

Type	Presenting symptoms
Retarded	Presents with: • immobility • mutism • staring • rigidity • refusal to eat • grimacing • negativism • waxy flexibility • echolalia or echopraxia • stereotypy • verbigeration • automatic obedience
Excited	• less frequent • periods of psychomotor agitation, life threatning with hyperthermia • altered level of consciousness • autonomic dysfunction
Mixed	• heterogenous presentation • patients may demonstrate symptoms of retarded and excited form
Malignant	• highly lethal form - demands early recognition (Mann 1986)

time, workup for ECT should be completed (Chap. 16: Neuromodulation Interventions).

If catatonic symptoms have not improved within 48–72 hours, or if symptoms of malignant catatonia emerge, treatment with ECT is recommended (Chap. 13: Involuntary Interventions; Chap. 16: Neuromodulation interventions). Resolution may occur within 1–2 treatments but may require 10–20 sessions.

If ECT is not available at the treatment location, a glutamate antagonist, amantadine, should be administered in a dose of 100 mg daily or memantine 10 mg daily titrated to 600 mg and 20 mg daily, respectively. If failure occurs, antiepileptic medications like carbamazepine and valproic acid should be administered 300–600 mg po daily or valproic acid 500–1500 mg po or IV daily. If an antiepileptic drug fails, treatment with an SGA in conjunction with lorazepam should be trialed. Aripiprazole 10–30 mg, olanzapine 2.5–10 mg, and clozapine 200–300 mg daily are the preferred among available SGAs [58].

15.6 Summary

SS, NMS, and catatonia are three syndromes that have several overlapping features. If untreated or unrecognized, each of these presentations can be life-threatening, especially in the geriatric population. Each syndrome has its own unique guidelines for treatment. The psychiatric inpatient setting affords the necessary resources to monitor and evaluate, in order to recognize distinguishing features of each syndrome, make an early diagnosis, and choose the specific treatment. A careful and timely approach will help to manage these patients and limit the progression of these life-threatening conditions. Table 15.7 summarizes the distinctions between SS, NMS, and catatonia, including key features of the Hunter serotonin toxicity criteria.

Table 15.7 Summary of SS, NMS, and catatonia

Syndromes	Serotonin Syndrome (SS)	Neuroleptic Malignant Syndrome (NMS)	Catatonia
Etiology	• Hyper-serotonergic state • Clinical symptoms related to increase in serotonin levels • Predictable adverse effect to medications • SSRIs the most common medications as a common causative agent	• Idiosyncratic reaction to medications	• Many possible etiologies • Neurological conditions, such as encephalitis, stroke • Psychiatric conditions such as schizophrenia, bipolar, major depressive disorders
Clinical Symptoms	• Triad of clinical symptoms - autonomic symptoms, altered mental symptoms, and neuromuscular excitation	• Hyperthermia- Temp >38 c • Extrapyramidal symptoms - tremors, parkinsonism • Altered mental state • Hypermetabolic state • Autonomic disturbance - Labile Heart Rate • Labile blood pressure • Tachycardia,Tachypnea	• Three out of 12 clinical symptoms, catalepsy, mutism stupor, agitation, stereotypy, negativism, waxy
Prodromal Symptoms	• Commonly have gastrointestinal symptoms, such as, nausea, vomiting and diarrhea	• Some patients have insidious alteration in mental status and other neurological signs in days prior to the clinical presentation	• EARLY abnormal motor signs: retardation, excitement, or mixed
Distinguishing Features	• Spontaneous/induced clonus and hyperreflexia - generally more pronounced in the lower limbs	• Hyperthermia • Lead pipe rigidity • Increased CK • Hyper-metabolic state	• Unusual motor symptoms like posturing are more typical of catatonia • Intense and uncontrollable emotions, behavior abnormalities such as stereotypy, negativism and automatic disobedience
Onset	• Typically within 24 hours of initiation of new medications or medication change typically SSRI	• Typically within 2 weeks of initiating medications or change in medications typically antipsychotics • Rarely, fulminant course, onset and peak of the illness course within 24 hours of initiating medications	• Typically acute and sudden
Screening scales/ criteria	• Hunters/ Strenbach criteria	• Francis-Yacoub NMS Rating Scale • Woodbury Staging Method for NMS	• Bräunig-Catatonia Rating Scale • Bush-Francis Catatonia Screening Instrument • Bush-Francis Catatonia Rating Scale • Rogers Scale • Northroff Scale • Catatonia Rating Scale
Treatment	• Withdraw all serotonergic agents • Supportive therapy • Benzodiazepines for myoclonus, seizures, hypertonia	• Withdraw all antipsychotic medications • Supportive therapy • Benzodiazepines • Dopaminergic agonists	• ECT and benzodiazepines • Treat underlying disorders - psychiatric, medical, neurological

Take-Away

- First: rule out acute syndromes, common in the geriatric population, such as delirium, substance intoxication, and anticholinergic toxicity.
- Review medication history and risk factors for SS, NMS, or catatonia.
- Attend carefully to clinical symptoms and their progression.
- Delineate history, symptoms, signs, which can differentiate SS, NMS, and catatonia.
- Institute treatment *specific* to the working diagnosis of SS, NMS, or catatonia.
- In the geriatric population, intervene early to minimize progression of SS, NMS, or catatonia.
- Continue to consider alternative diagnoses and adjust treatment accordingly.

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